Shaping the Future of Aneurysm Treatments

Livermore's shape-memorizing foams could be key to preventing life-threatening strokes.

EACH year, about 30,000 people in the U.S. die or suffer neurological damage from cerebral aneurysms, which form when a weak or thin region on a blood vessel in the brain bulges and fills with blood. An aneurysm can put pressure on a nerve or the surrounding brain tissue. If left untreated, an aneurysm can grow until it leaks or ruptures, spilling blood into the surrounding tissue and causing a hemorrhagic stroke. (See the box on p. 6.)

Stroke is the leading cause of disability in the U.S. and the third most common cause of death, after heart disease and cancer. Although strokes are most common in the elderly, they can occur in people of all ages, including children and infants. Significant strides have been made during the past few decades to lessen the stroke occurrence rate. According to the Centers for Disease Control and Prevention, the number of strokes has decreased steadily since the 1950s, primarily because more people are controlling their blood pressure and taking steps to prevent diseases that can lead to stroke. The decreased number can also be traced to better treatment options for people who have aneurysms.

Lawrence Livermore researchers are collaborating with colleagues from the University of California (UC) at Davis's Center for Biophotonics, Science, and

A multi-institution collaboration is widening the range of treatment options for cerebral aneurysms. Livermore members include (from left to right) Ward Small, Jane Bearinger, Jason Ortega, Thomas Wilson, and William Benett. (Not shown: Duncan Maitland.)

Technology and from UC Berkeley to develop safer, faster, and more cost-effective treatments for patients with cerebral aneurysms. The team's effort is funded primarily through Livermore's Laboratory Directed Research and Development (LDRD) Program, the National Institutes of Health (NIH), and the National Science Foundation.

Livermore scientist Duncan Maitland, who leads the team of 30, stresses the need for individualized approaches to the problem. "Cerebral aneurysms are not life-threatening until they begin pressing on the brain or burst," he states. "The problem is that few technical solutions currently exist for treating these aneurysms. Each aneurysm is unique and therefore requires customized treatment. We are widening the range of treatment options."

Little Aneurysm, Big Deal

Cerebral aneurysms occur more commonly in adults than in children, but they can occur at any age and are slightly more common in women than in men. They can result from birth defects, preexisting conditions such as high blood pressure and atherosclerosis (the buildup of fatty deposits in the arteries), or head trauma. Cerebral aneurysms are classified both by size and shape—small aneurysms have a diameter of less than 15 millimeters, while larger ones can exceed 50 millimeters.

"Before a larger aneurysm ruptures, the individual may experience a sudden and unusually severe headache, nausea, vision impairment, vomiting, or loss of consciousness, or the individual may experience no symptoms at all," says Livermore scientist Duncan Maitland. "A small, unchanging aneurysm will likely produce no symptoms while symptoms of a larger aneurysm usually occur suddenly and without warning. The larger an aneurysm becomes, the more likely it is to burst." While an estimated 30,000 aneurysms are diagnosed every year, perhaps as many as 10 times more go undetected.

"Our shape-changing foam-plug devices will be competing against the platinum coil technology that is used on 70 percent of treatable aneurysms," says Maitland. The remaining 30 percent are treated surgically with metal clips. An aneurysm is sometimes considered "untreatable" if it is exceedingly large or in a critical or hard-to-reach area of the brain. According to Maitland, approximately 40 percent of aneurysms are deemed "treatable"—aneurysms measuring outside of the range of 5 to 15 millimeters in diameter are usually not treated.

A brain aneurysm, also called a cerebral or intracranial aneurysm, is an abnormal bulging outward of an artery in the brain. As many as 1 in 15 people in the U.S. will develop a brain aneurysm during their lifetime.

Existing Aneurysm Treatments

Today, two treatment categories are available for aneurysms: surgical and nonsurgical. The goal of each is to prevent blood from entering the bulged-out section of the vessel, called the sac. Blood flow in this region increases pressure on the weakened vessel wall and heightens the risk of rupture.

Microvascular clipping, introduced in 1937, is the most common surgical treatment for cerebral aneurysms. For this treatment, a section of the skull is removed to expose the aneurysm under a microscope. The aneurysm is then completely closed off with a tiny (1- to 2-centimeter-long) metal clip to prevent bleeding or rupture and thereby protect nearby brain tissue from damage. If the aneurysm has grown enough to severely damage the blood vessel, the surgeon may elect to reroute the blood flow around the damaged area by grafting a piece of blood vessel from another part of the body.

The second procedure, called embolic coiling, is a nonsurgical treatment that was approved in the early 1990s for patients with inoperable aneurysms. For this treatment, a small plastic catheter is inserted in either the femoral (leg) or carotid (neck) artery. A contrast dye injected in the bloodstream through the catheter highlights the normal blood vessels and delineates the aneurysm. Continuous x rays of the patient's vascular system, provided by an imaging technique called fluoroscopy, help the surgeon maneuver a microcatheter into the aneurysm through the original catheter. Then tiny platinum wires—only slightly larger in diameter than a human hair—are deposited into the aneurysm. Finally, the wires take on a coil shape and induce blood clotting, which reduces or blocks blood flow in the sac.

Aneurysms with small entrance points, called narrow-neck aneurysms, are generally treated with the wire coils. A wide-neck aneurysm can also be treated with coils, but a stent or balloon must be used with the coils to prevent them from migrating to the parent vein or artery.

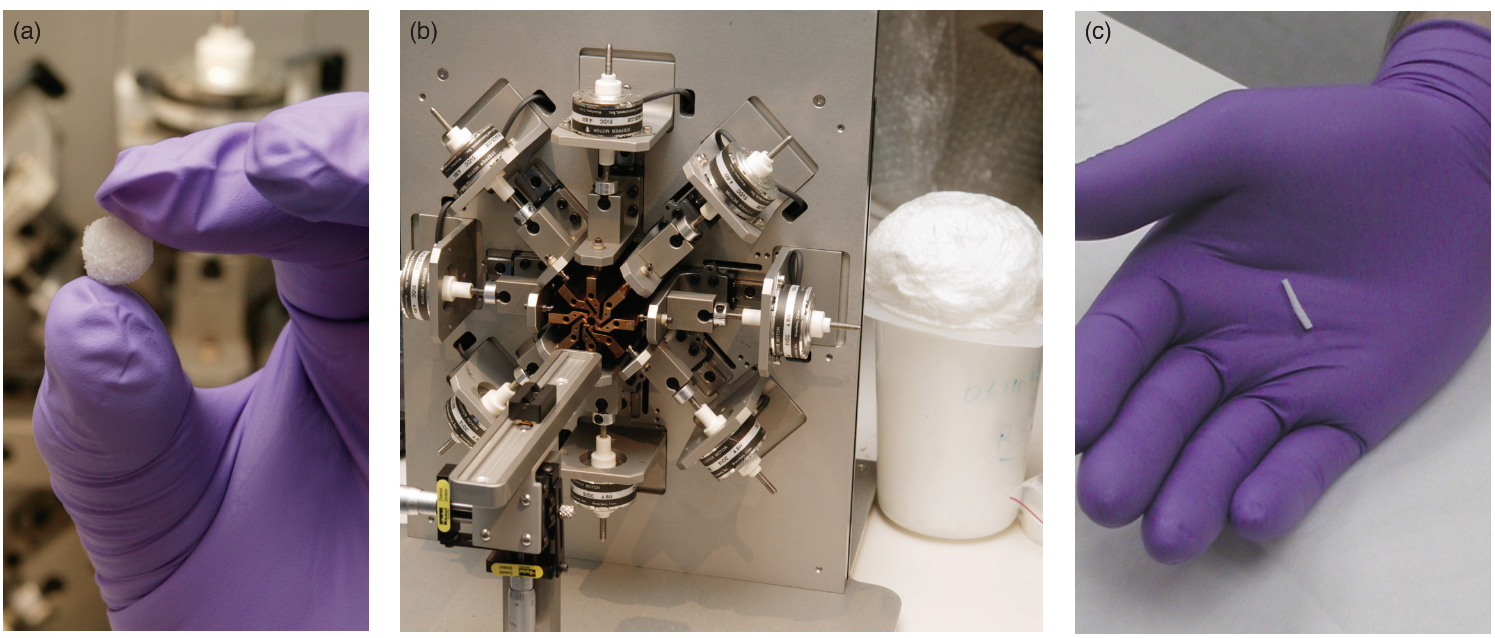
Doctors consider several factors when deciding which treatment option is best for a patient. These factors include the type, size, and location of the aneurysm; risk of rupture; patient's age, health, and medical history; and risk of treatment. Both surgical and nonsurgical methods have some drawbacks. "Using detachable coils to treat an aneurysm avoids many of the risks associated with surgery, but the treatment is a time-consuming process," says Maitland. "Because the coils can compact over time in the sac, 40 percent of the patients must have more coils implanted at a later date. In addition, each implanted coil has a 2-percent risk of bursting the aneurysm."

"Smart" Foams

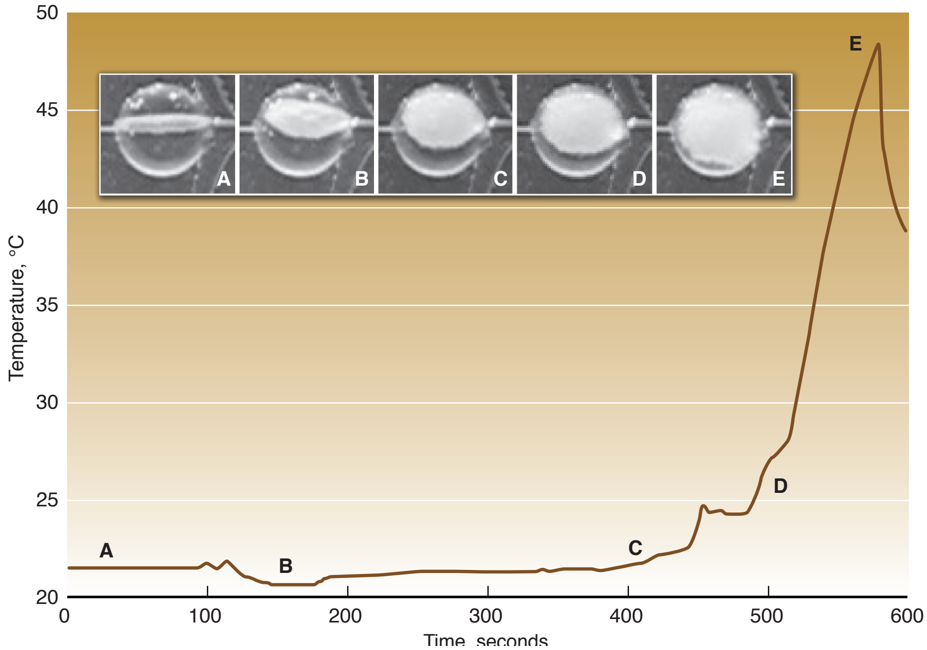
To address these shortcomings, Maitland's team developed an alternative treatment that isolates an aneurysm from the rest of the vascular system with one implanted device—a "plug" made from shape-memory-polymer (SMP) foam. SMPs are a class of polymeric materials that remember their primary (original) shape after being molded into a secondary (temporary) shape. Depending on the type of SMP, it can be altered from one shape to the next using heat, moisture, pH, or electric or magnetic fields. The Livermore-developed SMP foam plug is altered with heat.

Researchers first cut a plug out of the foam material to match the contours of an aneurysm. Then a crimping machine with heated blades compresses the foam plug into a stable secondary shape that can be fed through catheters via a fiber-optic cable to the aneurysm sac. Once the plug reaches the sac, it is heated with diode-laser light through the fiber-optic cable. Heating time could range from as little as 10 seconds to several tens of seconds, depending on the temperature at which the foam plug is designed to fully expand to its primary shape. As the plug expands, it absorbs blood, which congeals and forms clots to stop blood flow inside the aneurysm.

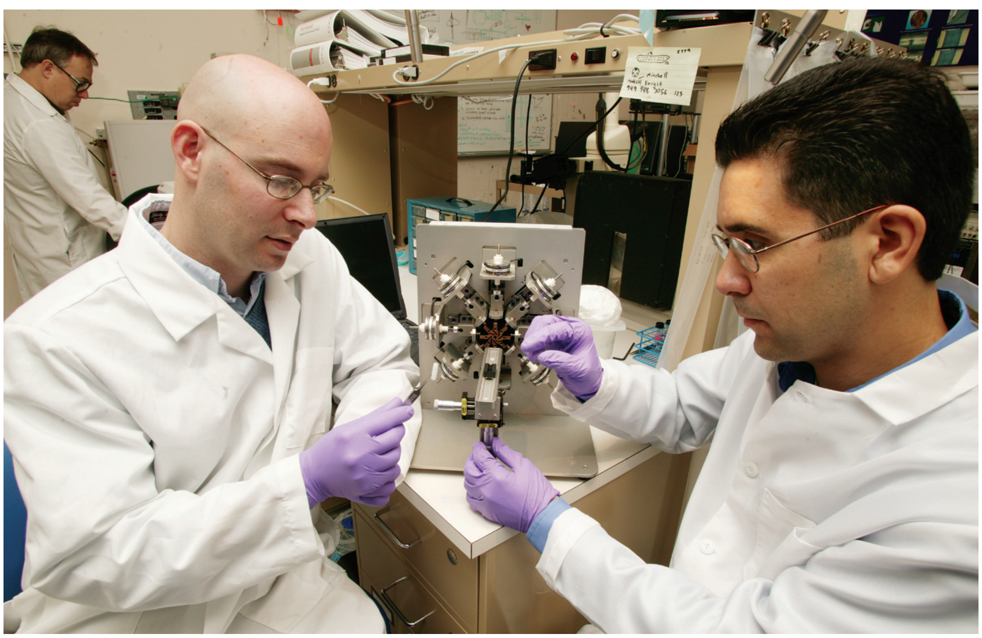
Although foam plugs have not been directly compared with platinum coils in statistically significant trials, studies with an in vitro aneurysm model demonstrated that the technology is efficient in filling the aneurysm sac. Livermore chemical engineer Thomas Wilson, a polymer materials expert, says, "A key feature of



Key to Livermore's shape-memory-polymer (SMP) foam technology is its compressibility. (a) A 10-millimeter-diameter spherical SMP foam plug is shown in its primary (original) shape. (b) An eight-blade cylindrical crimping machine with heated blades compresses the foam into a secondary shape. Next to the crimping machine is a foam "souffle" from which the plugs are first cut. (c) In its secondary shape, the foam can be fed through a catheter to the aneurysm.



This graph shows the expansion of an SMP foam plug from its compressed secondary shape to its original shape in response to temperature changes over a period of about 10 minutes (A to E).



Livermore researchers (left to right) Thomas Wilson, Ward Small, and Jason Ortega prepare shape-memory foam plugs for the crimping machine.

Livermore's SMP foam formulas is an open-cell structure, which makes the foam very porous and absorbent. We can make a foam plug that expands 80 to 90 times its compressed secondary shape."

Foam Versus Platinum

If Livermore's foam-plug procedure is approved for clinical trials, it could lead to a new, nonsurgical treatment option for patients. Wilson is optimistic because the foam plugs offer several advantages over platinum coils, including faster and more complete occlusion of the aneurysm and lower and more uniform stresses to the aneurysm wall, thereby decreasing the risk of hemorrhage.

"A doctor may have to add 20 platinum coils, one at a time, to fill the volume of an aneurysm that would require only one or two foam plugs to fill," says Maitland. "If the coils become compacted, the already vulnerable aneurysm wall may be reexposed to blood flow. We want to eliminate the need to treat an aneurysm more than once during a patient's lifetime."

The foam plugs may also prove safer than platinum coils, which can unravel and migrate into the blood vessel, potentially increasing the risk for aneurysm regrowth and rupture. "The foams are softer and have more tissuelike mechanical properties, so they are less likely to injure surrounding arterial tissue," says Wilson. What's more, each plug device can be customized to fit the distinct contours of the aneurysm being treated and is therefore more likely to stay in place.

In addition, unlike platinum coils, Livermore's foam plugs could be made from bio-absorbable material, which could help to heal the aneurysm. "We hope to develop a foam plug that can biodegrade into small molecules and be safely absorbed," says Wilson. "Over time, the device would essentially disappear and be replaced by human tissue."

Chemistry and Dynamics

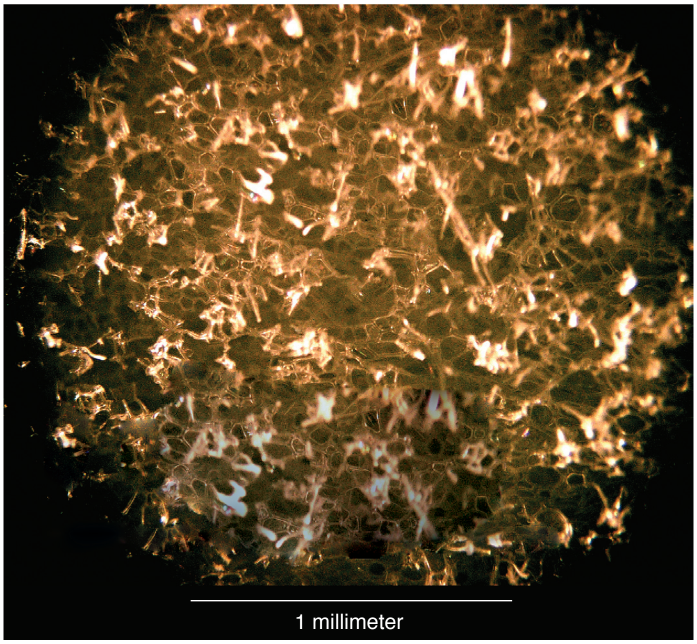
The Livermore SMP foam plugs are composed of four materials: hexamethylene diisocyanate; 2,2,4-trimethyl hexamethylene diisocyanate; 2-hydroxypropyl ethylenediamine; and triethanolamine. By adjusting the relative amounts of these materials, Wilson has developed three foam "recipes," which respond to various ranges of temperatures.

The temperature at which a compressed foam plug resumes its primary shape is called the glass transition temperature (T_g). Foams with a low T_g expand to their primary shape when heated from a cooler temperature to below normal body temperature (37°C); foams with a mid-range T_g expand when heated to 45°C; and foams with a high-range T_g expand when heated to 60°C and above. Wilson can alter each recipe to allow for greater heating and cooling margins as necessary. When the T_g of a foam plug is above normal body temperature, a laser or other heating mechanism is required to restore the foam's primary shape.

The Livermore group is working with UC Berkeley to develop a measurement system that records aneurysm-wall temperatures during laser delivery of the implanted plug devices. The system will help researchers assess the effects on arteries from heating the foam plugs internally. "Foams with a transition temperature just above normal body temperature are optimal because they won't require much additional heat to expand," explains Wilson. "The goal is to reduce the foam's transition temperature to minimize internal damage to tissue."

Livermore mechanical engineer Jason Ortega is conducting computational fluid dynamics simulations, which will answer questions about the foam-plug implant procedure. Specifically, the simulations give researchers a look at the interaction of the foam plug with the artery wall. Ortega has modeled blood flow within a simulated aneurysm before, during, and after treatment with an SMP foam plug. He has obtained detailed information about the velocity, pressure, and traction force that the fluid (blood) exerts on the adjacent artery wall. Ortega notes, "This type of high-resolution, instantaneous data cannot be obtained from current in vivo measurement techniques such as computerized axial tomography and magnetic resonance imaging."

Wilson says, "The simulations give us information that would be experimentally difficult, time-consuming, and potentially impossible to obtain otherwise. They also help us address the concerns of grant reviewers, veterinarians, and physicians prior to beginning animal and clinical studies." The simulations, in combination with animal testing, should help demonstrate that Livermore's expandable foam technology is a better alternative to platinum coils.



An optical micrograph shows the open cell structure of a Livermore-designed SMP foam. This urethane-based SMP exhibits properties superior to SMPs commercially available today.

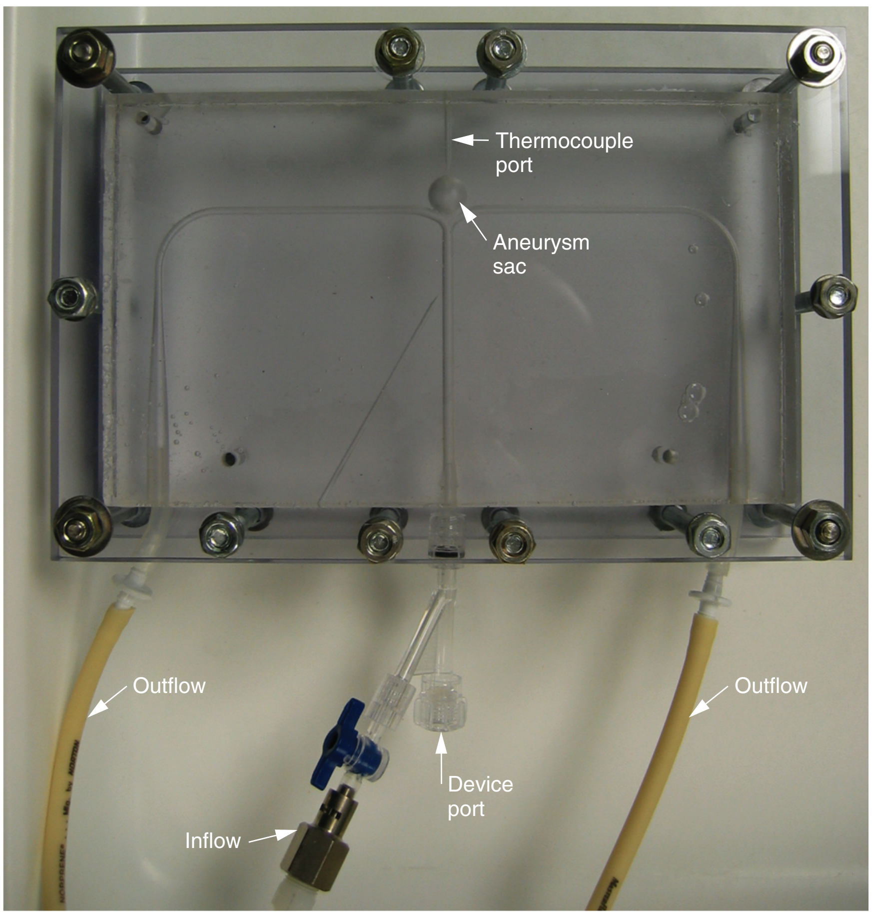
Prototype Testing

Bioengineer Ward Small IV leads Livermore's prototype-testing efforts. In a preliminary study, he used a silicone rubber model fabricated by the Engineering Technologies Division to simulate an aneurysm and the surrounding arrangement of blood vessels, or vasculature. (See the figure on p. 10.) Water was used to simulate the blood flow. Small was successful in deploying a single SMP foam plug to occupy a 11-millimeter aneurysm. His study also showed that varied flow rates affected foam-plug deployment. Low flow resulted in slow, full expansion with minimal temperature increase at the aneurysm wall, while high flow resulted in incomplete expansion. Future efforts are planned to resolve these expansion issues.

According to Maitland, the foam plugs will require modifications before they are ready for clinical trials. In particular, an effort is under way to design lower density foam plugs capable of greater volume expansion. At this time, the foam plugs measure 1,800 micrometers in diameter when compressed to the secondary shape—too large to be delivered through a typical microcatheter with a diameter of 300 to 600 micrometers. If additional volume is removed (for example, from holes, dimples, and channels in the foam), Maitland says that foam devices capable of filling a 10-millimeter aneurysm could possibly be compressed to 500 micrometers in diameter without sacrificing clotting performance.

Small also tested a Livermore-developed stent and plug device designed to treat fusiform, or wide-neck, aneurysms. These aneurysms pose a problem for wire-coil and foam-plug treatments alike because the implanted devices can easily dislodge through the wide-neck openings. Small's prototype consists of a stent, or tube, on which a foam plug has been grafted. After deploying the device into an in vitro aneurysm model, Small observed that the foam-plug portion of the device successfully expanded and filled the fusiform aneurysm, while the stent prevented the plug from migrating out of the aneurysm. At the same time, the stent maintained an open channel for fluid to flow in the blood vessel.

Wilson has also been working with researchers from UC Davis to test the biocompatibility of the SMP foams with pig and human blood. Both blood types were shown to be compatible with the foams.



Livermore researchers fabricated a silicone rubber model to simulate blood flow, an aneurysm, and surrounding blood vessels. A catheter enters through the device port, and the foam plug travels through it to the aneurysm sac, which is about 11 millimeters in diameter. A thermocouple port monitors the temperature in the sac.

Years of Research

The Livermore group was formed in 1996 to work with Micrus Endovascular Corporation, a U.S.-based neurointerventional device company. The purpose of this effort was to develop a device that could quickly release platinum coils inside an aneurysm and prevent a hemorrhagic stroke. The researchers created a device called an SMP microgripper, which was successful in clinical tests. In 1999, the group was one of 15 in the nation to receive an award that recognizes federal laboratory employees who have accomplished outstanding work in the process of transferring a technology to the commercial marketplace. It also received LDRD funding to continue working on applications for treating both hemorrhagic (aneurysm-induced) and ischemic (blood-clot-induced) strokes.

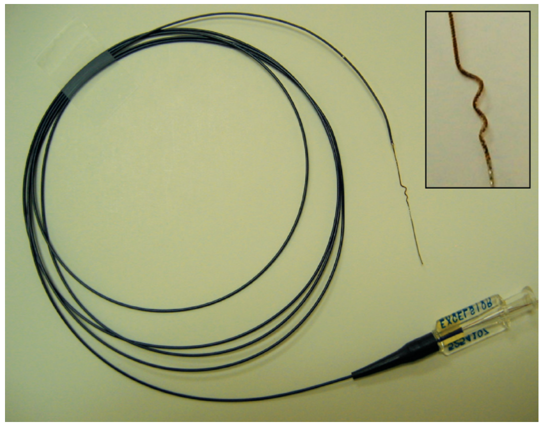
In 1999, while Maitland was using a plumber's snake to unclog a drain in his house, he came up with an idea to develop a mechanism that could work similarly on blood clots in the brain. In 2000, he received a grant from the Department of Energy's Office of Biological and Environmental Research to fund the research and development of a corkscrew wire made of SMP materials. This device for spearing a blood clot is designed to enter the body through a catheter as a straight wire. The wire is then heated with a laser, which causes it to recoil. As the wire is withdrawn through the catheter, it "grips" the clot to remove it from the blood vessel. Tests showed the wire could hold a clot securely against a flow of liquid more than 10 times the blood pressure normally found in the brain. Maitland's team successfully took the corkscrew through pilot animal studies and is currently developing an advanced version.

In 2002, the team shifted its focus from treating blood clots back to treating aneurysms when Wilson began developing SMP foams using commercial formulas. The National Institute of Biomedical Imaging and Bioengineering at NIH funded the initial research and development of these expandable foams in 2003. However, after two years of experimenting with commercial SMP formulas, the effort was abandoned in 2005 when Wilson and Livermore biomedical engineer Jane Bearinger began developing novel SMP formulas for bulk materials. A subset of these SMPs were then developed into foams that could expand 80 to 90 times their compressed volume—far exceeding the expandability limits of commercial formulas, which could only expand to 30 times their compressed volume.

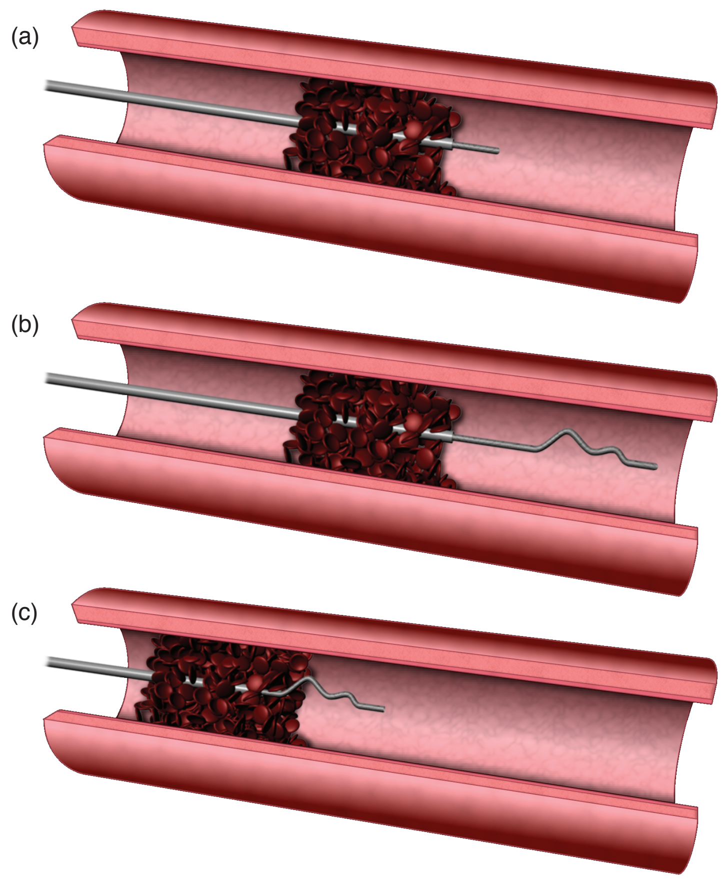
Maitland points to the synergy between SMP foam research and homeland security, a major Livermore mission. "Our expertise in the fabrication of complex devices and in energy–materials interactions can transfer into biosecurity and sensor applications relating to nuclear weapons."

Shape-Changing Team Dynamics

In 2008, the team received five years of NIH funding to test Livermore's plug devices on animals at Texas A&M University. As a result, Wilson will continue leading the team's research efforts



This Livermore-developed SMP corkscrew, or thrombectomy, device removes blood clots that can cause ischemic strokes.



The delivery of an SMP corkscrew device to remove a blood clot occurs in three distinct phases. (a) In its secondary straight shape, the device is delivered through a catheter to pierce the clot. (b) The device is then heated with a diode laser, transforming it back to its primary corkscrew shape. (c) Finally, the device captures and removes the clot as it is retracted.

Livermore's Duncan Maitland will test SMP foam plugs on animals at the Texas Institute for Preclinical Studies, a large-animal research facility under construction at Texas A&M University. (Artist rendering courtesy of Texas A&M University.)

at Livermore, while Maitland is in Texas working with a team of veterinary surgeons to test the plug devices on animals.

In addition, Maitland will continue to focus on the advancement of SMP foams originally developed at Livermore. He notes that SMPs are receiving a great deal of scientific interest for applications that range far beyond medicine. "Our SMP foams could be used to deploy large structures in space such as solar panels," says Maitland. "They could also be used to make expandable packing materials to protect a delicate instrument during shipping." Another application could be self-expanding insulation in clothing.

The team is now in discussions with companies to license the SMP foams for treating aneurysms, although it may be some years before Livermore's foam technology materializes into medical devices. Wilson is optimistic that Livermore's SMP foam technology holds the potential to radically improve the prognosis for those with aneurysms. Bearinger says, "Our technology can leverage existing delivery systems to transport a foam plug to an affected vessel. The foam plug will fill more of the aneurysm than present therapies and encourage clotting, thereby blocking off the defective vessel region." Maitland adds, "Cerebral aneurysms are an undertreated medical problem. Our new foam technology has the potential to make dramatic gains in survivability and quality of life."

—Kristen Light

Key Words: aneurysm, embolic coiling, foam, hemorrhagic stroke, laser, shape-memory polymer (SMP).

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